Remarks

The Amendments

Claims 1, 4, and 8 have been amended. Claims 13-15 and 20-25 were previously withdrawn without prejudice as drawn to a non-elected invention.

Claim 1 was amended to recite that the test agent modulates the expression or ATPase activity of PSMC2. Support for the amendment is found in the specification at, for example, pages 2-3 and 22. Claims 1 and 8 were amended merely to provide proper antecedent basis.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

Claim Objections

Claim 4 is objected to because it depends from claim 1 and recites a "candidate test agent", which term is not present in claim 1. Claim 4 has been amended to recite a "test agent", thereby obviating the objection. Applicants respectfully request withdrawal of the objection to claim 4.

Claim 3 depends from claim 1 and is objected to as being dependent upon a rejected claim base, but would be allowable if rewritten in independent form including all of the limitations and any intervening claims. For the reasons provided herein, we believe claim 1 is free of the art.

Rejections under 35 USC 102

Claims 1, 2, 4, and 6 were rejected under 35 USC 102(e) as being anticipated by US Patent No. 6,831,099 ("Crews") as evidenced by Tanahashi et al (J. Biol. Chem., 2000, 275:14336-14345). Applicants respectfully traverse the rejections.

The Office alleged that in Example 8 Crews teaches a method comprising the steps of: (a) providing an assay system (comprising HUVEC or HeLa cells); (b) contacting the assay system with a test agent (i.e., epoxomicin or lactacystin); and (c) detecting a difference in the activity of the assay system (i.e., levels of intracellular ubiquinated proteins and p53 levels). In addition, the Office alleged that in Examples 12 and 13 Crews teaches: (a) providing an assay system (comprising bovine aortic endothelial (BAE) cells); (b) contacting the assay system with a test agent (epoxide derivative proteasome inhibitors); and (c) detecting a difference in the activity of the assay system (i.e., cell proliferation, chymotrypson-like activity, and peptidylglutamyl peptide hydrolyzing activity) in the presence or absence of the test agent.

The Office stated that the methods described by Crews necessarily identify the test agent as a candidate RB modulating agent given that they detect a difference in the activity of the assay system in the presence or absence of the test agent. Furthermore, according to the Office, Tanahashi evidences that eukaryotic cells, including HeLa cells, contain 26S proteasome, which inherently comprises subunit C2. Therefore, the Office concluded that the assay systems taught in the method of Crews inherently express C2 (PSMC2) and comprise C2 polypeptide.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987); *In re Recombinant DNA Technology Patent and Contract Litigation*, 30 USPQ2d 1881 (S.D. Ind.1993) ("A patent is anticipated only if all the elements and limitations of the claims are found within a single, prior art reference. No difference may exist between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of invention."); *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) (All elements of the claimed invention must be contained in a single prior art disclosure and must be arranged in the prior art disclosure as in the claimed

invention); M.P.E.P § 2131. The identical invention must be described or shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir. 1990); M.P.E.P. § 2131.

Applicants submit that Crews does not anticipate the present invention because it fails to teach each and every element as set forth in the claims. Claim 1, as amended, recites a method for identifying a candidate RB pathway modulating agent, comprising (a) providing an assay system comprising a PSMC2 polypeptide or nucleic acid; (b) contacting the assay system with a test agent that modulates the expression or ATPase activity of PSMC2; (c) determining the activity of the assay system in the presence or absence of the test agent; and (d) identifying the test agent as a candidate RB pathway modulating agent by detecting a difference in the activity of the assay system in the presence or absence of the test agent.

Initially, Applicants submit that Crews fails to even mention PSMC2 or the RB pathway, much less recognize a connection between PSMC2 and the RB pathway. In the absence of such teaching, Crews fails to teach or suggest a screening assay comprising PSMC2 to identify a candidate RB pathway modulating agent. Further, among other things, claim 1 requires the step of contacting the assay system with a test agent that modulates the expression or ATPase activity of PSMC2. As taught in the instant specification and known in the art, the 26S proteasome comprises, among other things, a 20S core complex and an ATP-dependent 19S regulatory complex. Each complex is made up of several different protein subunits. PSMC2 is one of the subunits located in the 19S regulatory complex having ATPase activity. Crews is directed to the use of methods and compounds for modifying catalytic subunits found in the 20S core complex of the 26S proteasome. In particular, Crews provides compounds, including epoxides, epoxide derivatives, and peptide aziridines, that inhibit the chymotrypsin-like, trypsin-like, and peptidylglutamyl peptide hydrolyzing activities of the 20S core complex. In Example 1, Crews teaches that the described epoxide compounds inhibit the activities of the LMP7, MECL1, and Z subunits of the 20S core complex. Given that Crews is concerned only with regulation of the 20S core complex, it fails to contemplate modulating any of the subunits of the 19S complex, much less modulating the expression

or ATPase activity of the PSMC2 subunit. Therefore, Crews fails to teach or suggest an assay system that employs the use of a test agent to modulate the expression or ATPase activity of PSMC2. Applicants submit that Crews does not anticipate the present invention because it fails to teach each and every element as set forth in the claims.

Tanahashi merely teaches that HeLa cells contain 26S proteasome, but provides no further teaching with respect to PSMC2 or the modulation of PSMC2 expression or ATPase activity. Furthermore, for the sake of clarification, Applicants point out that the anti-C2 antibodies taught by Tanahashi (and mentioned by the Office) are directed against subunit HC2 (PSMA1) located on the 20S core complex, not against PSMC2 located on the 19S regulatory complex. Hendil et al., Biochem J., 305: 245-252 (1995); Tipler et al., Mol. Human Reprod., 3: 1053-1060 (1997).

Therefore, given that neither Crews nor Tanahashi even mentions PSMC2 or the modulation of PSMC2, much less recognizes a connection between PSMC2 and the RB pathway, neither reference teaches or suggests the claimed methods of identifying a candidate RB pathway modulating agent using an assay system comprising a PSMC2 polypeptide and a test agent that modulates the expression or ATPase activity of PSMC2. For the reasons set forth above, Crews (as evidenced by Tanahashi) does not anticipate the claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejections based on Crews.

Claims 1, 4, and 5 were rejected under 35 USC 102(e) as being anticipated by Hoffman et al., (J Biol Chem, 1996, 271:32538-32545) ("Hoffman") as evidenced by Tanahashi et al (J. Biol. Chem., 2000, 275:14336-14345). Applicants respectfully traverse the rejections.

The Office alleged that Hoffman teaches a method comprising the steps of: (a) providing an assay system (comprising 26S proteasome isolated from rabbits); (b) contacting the assay system with a test agent (i.e., small molecule inhibitors of proteolysis); and (c) detecting a difference in the activity of the assay system (i.e., ATPase activity, ATP hydrolysis). In addition, the Office alleged that Hoffman teaches that the 26S proteasome contains a 20S proteasome and, as evidenced by Tanahashi, the

20S proteasome inherently comprises the C2 subunit. Therefore, the Office concludes that the assay system taught in Hoffman inherently comprises the C2 polypeptide.

As discussed above, the Office errs in its identification of the C2 subunit as the PSMC2 subunit. Regardless, Applicants note that Hoffman teaches that the 26S proteasome contains a 20S regulatory complex ("RC"), which, although not expressly taught by Hoffman, includes the PSMC2 subunit.

Applicants submit that Hoffman fails to anticipate the instant invention. Although Hoffman generally discusses the 19S (20S, in Hoffman) regulatory complex, it fails to specifically identify or teach the individual subunits of the RC, including failing to identify PSMC2. Thus, Hoffman fails to mention PSMC2 or the RB pathway, much less recognize a connection between PSMC2 and the RB pathway. In the absence of such teaching, Hoffman fails to teach or suggest a screening assay comprising PSMC2 to identify a candidate RB pathway modulating agent. Furthermore, Hoffman fails to teach the step of contacting the assay system with a test agent that modulates the expression or ATPase activity of PSMC2. Although Hoffman mentions small molecule compounds, including hemin, NEM, vanadate, and aurintricarboxylic acid, that inhibit ATPase activity in the 26S proteasome and RC, it fails to identify any specific substrates for these molecules in the 26S proteasome or RC. Thus, there is no teaching or suggestion in Hoffman of any test agent(s) that modulates the expression or ATPase activity of PSMC2. In the absence of such teaching, Hoffman fails to teach or suggest an assay system that employs the use of a test agent to modulate the expression or ATPase activity of PSMC2. Applicants submit that Hoffman does not anticipate the present invention because it fails to teach each and every element as set forth in the claims.

As discussed above, Tanahashi merely teaches that HeLa cells contain 26S proteasome, but provides no further teaching with respect to PSMC2 or the modulation of PSMC2 expression or ATPase activity. Given that neither Hoffman nor Tanahashi even mentions PSMC2 or the modulation of PSMC2, much less recognizes a connection between PSMC2 and the RB pathway, neither reference teaches or suggests the claimed methods of identifying a candidate RB pathway modulating agent using an assay system comprising a PSMC2 polypeptide and a test agent that modulates the expression or ATPase activity of PSMC2. For the reasons set forth above, Hoffman (as evidenced by

Tanahashi) does not anticipate the claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejections based on Hoffman.

Claims 1 and 7 were rejected under 35 USC 102(e) as being anticipated by Kania et al., (Eur J Biochem, 1996, 236:510-516) ("Kania"). Applicants respectfully traverse the rejections.

The Office alleged that Kania teaches the claimed methods because it teaches a method comprising (a) providing an assay system comprising 20S proteasome isolated from rabbits; (b) contacting the assay system with antibodies that bind C2 (i.e., mAB GD6 and MCP20); and (c) detecting a difference in the activity of the assay system (i.e., peptide hydrolysis; trypsin-like and peptidylglutamyl hydrolyzing activity) in the presence or absence of the test agent. The Office further alleged that Kania teaches that the GD6 and MCP20 antibodies used in the assay system bind to C2, wherein the GD6 antibody was shown to bind C2 and inhibit proteasome activity (p. 514, col. 1). The Office therefore concluded that the assay system taught by Kania inherently comprises a C2 (PMSC2) polypeptide.

Initially, Applicants submit that the Office has erred in stating that the GD6 and MCP20 antibodies bind to the PMSC2 subunit. Kania teaches at page 514 that antibodies MCP20 and GD6 bind to the same proteasome subunit at different epitopes, which proteasome subunit was identified as proteasome subunit HC2. (see also Table 1). However, proteasome subunit HC2, also known as proteasome (prosome, macropain) subunit alpha type 1 (PSMA1) is not PMSC2. HC2, or PSMA1, is a protein located in the 20S core complex having two isoforms of 263 and 269 amino acids. See GenBank NM_148976; NP_683877 and NM_002786; NP_002777. In contrast, proteasome (prosome, macropain) 26S subunit ATPase 2 (PMSC2) is a protein of 433 amino acids located in the 19S regulatory complex. See GenBank NM_002803; NP_002794. Furthermore, Kania specifically states that the GD6 antibody does not bind to or block proteasome activation by the 19S regulator (the complex in which the PMSC2 subunit is located). See Abstract. Thus, neither the MCP20 antibody nor the GD6 antibody binds to or modulates the activity of PSMC2.

As indicated by the Office, the investigators in Kania performed peptidase assays

containing purified 20S proteasomes and PA28 from rabbit reticulocytes in the presence or absence of various monoclonal antibodies against different 20S proteasome subunits (Table 1) to determine the antibody's ability to reduce PA28 stimulation of chymotryosinlike activity. Only the GD6 antibody, which binds to HC2 in the 20S complex, was found to reduce proteasome 20S peptidase activity (it also blocked activation of the trypsin-like and peptidyl glutamyl hydrolyzing activity) (see Table 2). Contrary to the Office's assertion, the described assays do not teach or suggest the claimed methods. First, these assays of Kania employed the use of purified 20S core complex, which does not include the PSMC2 subunit. Thus, the PSMC2 polypeptide or nucleic acid was not even present in the assay system. Second, as discussed in detail above, the antibodies (ie test agents) used in the assay system do not bind to or modulate the activity of PSMC2.

Although not discussed by the Patent Office, Applicants note that Kania mentions other peptidase assays comprising a 20S core -19S regulatory proteasome complex (which presumably includes the PSMC2 subunit) performed in the presence of various antibodies, including an antibody against the PSMC2 subunit (the α-MSS1 antibody mentioned on p. 514). This teaching, however, also does not anticipate the instantly claimed methods for the reasons set forth below.

First, as with the other cited references, Kania fails to mention PSMC2 or the RB pathway, much less teach or suggest a connection between them. In the absence of such teaching, Kania fails to teach or suggest a screening assay comprising PSMC2 to identify a candidate RB pathway modulating agent. Also, as previously discussed, claim 1 requires the step of contacting the assay system with a test agent that modulates the expression or ATPase activity of PSMC2. Although Kania suggests an assay in which an anti-PSMC2 antibody is included, it in no way teaches or suggests contacting the assay system with a "test agent that modulates the expression or ATPase activity of PSMC2", as required by the instant claims. As stated earlier, Kania does not mention PSMC2 or discuss its ATPase activity and is therefore not interested in a test agent that modulates the ATPase activity of PSMC2. Kania was studying ATP-dependent peptidase activation of the 20S proteasome core complex by the 19S regulatory complex and employed an anti-PSMC2 antibody merely to see if the PSMC2 subunit was involved in 19S – 20S proteasome

complex formation. See p. 514, right column. However, even in this regard, Kania found that the anti-PSMC2 antibody had no effect whatsoever on the peptidase activity of the proteasome complex, indicating that PSMC2 is not involved in 19S proteasome binding. Furthermore, there is no evidence whatsoever that the anti-PSMC2 antibody inherently modulated the ATPase activity of PSMC2. In fact, if anything, Kania's results suggest the opposite - given that the enzymatic activity of the proteasome complex was not affected by the anti-PSMC2 antibody, it suggests that the antibody had no effect on the function (i.e., ATPase activity) of PSMC2. Given that Kania fails to mention the PSMC2 subunit and certainly fails to contemplate modulating the expression or ATPase activity of the PSMC2 subunit, it necessarily fails to teach or suggest an assay that employs the use of a test agent to modulate the expression or activity of PSMC2. Applicants submit that Kania does not anticipate the present invention because it fails to teach each and every element as set forth in the claims.

In view of the fact that Kania fails to teach PSMC2 or the modulation of PSMC2, much less recognize a connection between PSMC2 and the RB pathway, it fails to teaches or suggest the claimed methods of identifying a candidate RB pathway modulating agent using an assay system comprising a PSMC2 polypeptide and a test agent that modulates the expression or activity of PSMC2. For the reasons set forth above, Kania does not anticipate the claimed invention. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejections based on Kania.

If the Examiner has any questions regarding this response, she is invited to call the undersigned attorney.

Respectfully submitted,

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